Remarks/Arguments:

Claim rejections 35 U.S.C. § 112

Applicants are pleased to note that the Examiner has indicated that the cancellation of "ester or amide thereof" has overcome the previous objection item (a). Regrettably, however, the Examiner is maintaining the previous rejection of claim 27 under 35 USC 112, second paragraph and has raised a new "scope of enablement" rejection under 35 USC 112, first paragraph.

Rejection of Claims 20, 27, 30, 34-39 and 41-44 Under § 112, First Paragraph

Considering firstly the scope of enablement rejection, the Examiner acknowledges in paragraph 1 on page 2 of the Office Action that the specification is enabling for making and using compounds of formula (IID) wherein R^{64} is unsubstituted phenyl or such rings substituted by simple groups such as halogen, alkoxy, alkyl, nitro, and CF_3 but asserts that the specification is not enabling for compounds of formula (IID) wherein R^{64} is a phenyl group that is extensively substituted, and further substituted, nor for compounds of formula (IID) wherein R^{64} is optionally substituted heterocyclyl.

This assertion appears to be based, at least in part, on the Examiner's view that the only compounds of formula (IID) exemplified are the compounds in Tables 2 and 3 (in which the phenyl group (of R^{64}) is not substituted) as stated in the paragraph bridging pages 3 and 4 of the Official Action.

Applicants would point out, however, that of the compounds listed in Table 2, only compounds 95-98 fall within the scope of formula (IID) (albeit these do indeed have R^{64} as unsubstituted phenyl). Moreover, the compounds of Table 3 are, in fact, excluded from the present scope of the claims as X is O and not NH as called for in present Claim 20. Compounds of formula (IID), including compounds in which R^{64} is substituted phenyl or optionally substituted heterocyclyl, are however clearly exemplified in Tables 4 and 5 on pages 37-39 of the specification (note that R^{64} is a subset of R^9; see the definition of R^9 on page 3, lines19-20 of the specification). For example, in Table 4, R^9 (or R^{64}) is a substituted or unsubstituted heterocycle in examples 106, 107, 109, 116, 121, 122, 123, 127, 133, 137, 138, 148, 150, 151, 154, 161, and 162, and a substituted phenyl in examples 102, 103, 110, 111, 113, 114, 115, 120, 125, 126, 129, 130, 131, 134, 135, 140, 142, 144, 145, 146, 147, 149, 152, 156, 157, 158, 159, 160, 163, 164. In Table

5, R^9 (or R^{64}) is a substituted or unsubstituted heterocycle in examples 171, 172, 174-177, 186, and 189 and a substituted phenyl in examples 166, 169, 178, 179, 183, 184, 185, and 188.

Based on the numerous working examples in Applicants' specification, Applicants would submit that restricting the scope of the claims to compounds in which R^{64} is phenyl optionally substituted with simple substituents would be unduly limiting. However, in order to expedite prosecution, Applicants have amended the claims to exclude the possibility that a phenyl or heterocyclyl ring represented by R^{64} can itself be substituted by another ring and also to exclude the 'substituents on substituents' which the Examiner has objected to. Thus, in the claims, as amended, when R^{64} is a phenyl or a heterocycle, it can be substituted with one or more groups selected from nitro, halo, carboxy, cyano, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkylthio, acetoxy, acetamido, hydroxy, aminosulphonyl, C_{1-4}alkylsulphonyl, and trifluoromethyl. Applicants submit that Tables 4 and 5 show many examples in which R^{64} is a substituted or unsubstituted phenyl and a substituted or unsubstituted heterocycle and that the substituents for phenyl or a heterocyclic group in the claims, as amended, are simple groups many of which are exemplified in the specification. Therefore, Applicants request that the rejection of Claims 20, 27, 30, 34-39 and 41-44 under 35 U.S.C. § 112, first paragraph be reconsidered and withdrawn.

Rejection of Claims 20, 27, 30, 34-39 and 41-44 Under § 112, Second Paragraph

The Examiner has rejected Claim 20, and the claims depending therefrom, stating that the variable "ar" in several moieties has no definition and it is unclear what the scope of "ar" is.

Applicants have amended Claim 20 to replace the term "arC_{1-10}alkyl" with the term "aralkyl." The term "aralkyl" is defined on page 5, line 21 of the specification as "aryl substituted alkyl groups." Aryl groups are defined on page 5, lines 9-10 and alkyl groups are defined on page 5, lines 1-3 of the specification.

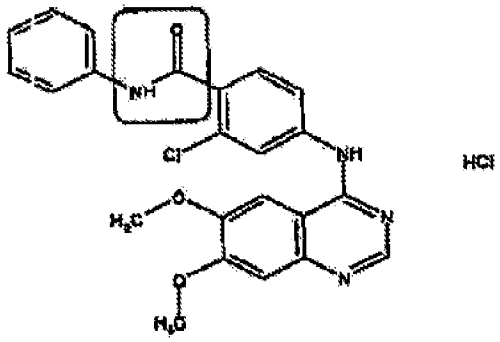
Applicants have also amended Claim 20 to replace the term "arC_{1-10}alkyloxy" with the term "aralkyloxy." As explained in the preceding paragraph, the term "aralkyl" is defined in the specification. The "oxy" portion of the term "aralkyloxy" is known in the art to indicate that a group is attached to another moiety via an oxygen atom (e.g. benzyloxy).

The Examiner has rejected Claim 27 stating that the last step of "converting a group R^1, R^2, R^3 or R^4 respectively to a different such group" is unclear as to which group gets converted to which and by what means.

Applicants have amended Claim 27 to indicate that a precursor group $R^{1'}$, $R^{2"}$, $R^{3"}$, or $R^{4'}$ may be converted to a group R^1, $R^{2'}$, $R^{3'}$ or R^4 respectively making it clear that the precursor group $R^{1'}$ may be convert to an R^1 group, the precursor group $R^{2"}$ may be converted to $R^{2'}$, the precursor group $R^{3"}$ may be converted to $R^{3'}$ and the precursor group $R^{4'}$ may be converted to R^4. Thus, a person of ordinary skill in the art could select an $R^{1'}$ precursor group, for example, which could be converted to a desired R^1 group by means known in the art. May articles and texts books describe precursor groups and means for converting them into a desired functional group (for example see Green and Wuts, "Protecting Groups in Organic Synthesis, 3rd edition,"(1990), John Wiley and Sons, Inc.). Thus, Applicants respectfully submit that Claim 27, as amended, meets the requirements of 35 U.S.C. § 112, second paragraph.

Rejection of Claims 20, 27, 30 and 34-39 and 41-44 Under 35 U.S.C. § 103(a) Over Brown *et al.*, WO 96/15118

The Examiner has maintained the rejection of claims 20, 27, 30 and 34-39 and 41-44 as being unpatentable over Brown *et al.*, WO 96/15118 (hereinafter "Brown"). In this rejection, the Examiner selected Example 11 on page 54 of Brown (see structure below) from 52 specifically disclosed compounds in the reference and used it as a starting point for making modification to come up with Applicants' claimed compounds. Using Example 11 of Brown as a starting point, the Examiner states that the disclosed compound differs from Applicants' claimed compounds in that it has a carbamoyl group instead of an amido group in the position circled in Example 11 below. The Examiner then reasoned that this modification would be obvious because Brown et al. teaches that X at the position of the carbamoyl can be selected from a list of 19 different divalent linking groups (many of which contain additional variable substituents themselves) one of which is an amido group.



Example 11

As Applicants have argued previously, we believe that this rejection is not well founded. Compared to Example 11 of Brown, the presently claimed compounds differ in the following respects:

(i) Example 11 of Brown has carbamoyl attached to the aniline group rather than an amindo as in the corresponding side chain of the presently claimed compounds;

(ii) $R^{3'}$ in the present compounds cannot be methoxy; and

(iii) Substituents R^7 and R^8 in the presently claimed compounds must be located at specifically defined positions on the phenyl ring.

It remains our position that Brown provides no motivation to select Example 11 from the numerous disclosed examples or any motivation to make these changes.

The Court of Appeals for the Federal Circuit has ruled in *Takeda Chemical Industries, LTD. v. Alphapharm PTY., LTD*, 492 F.3d 1350 (Fed. Cir. 2007) that Alphapharma failed to establish a case of *prima facie* obviousness when they failed to prove that a person of ordinary skill in the art would have been motivated to select a particular compound from a reference containing ninety compounds as a starting point for modifications that were needed to make Takeda's patented compound. The court states the following:

> Because Alphapharm's obviousness argument rested entirely on the court making a preliminary finding that the prior art would have led to the selection of compound b as the lead compound, and Alphapharm failed to prove that assertion, the court did not commit reversible error by failing to apply a presumption of motivation. We thus conclude that the court did not err in holding that

Alphapharm failed to establish a *prima facie* case of obviousness. *Takeda v. Alphapharm*, 492 F.3d 1350, 1360.

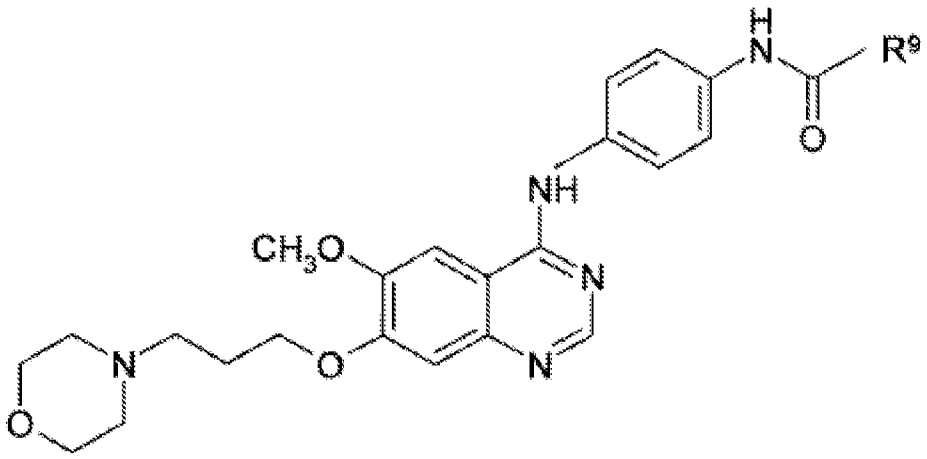
In the instant case, the Examiner has selected Example 11 from a reference that contains 51 exemplified compounds as a starting point for making modifications to arrive at applicants' claimed compounds. There is nothing in the reference to suggest that Example 11 is a preferred compound for treating cancer and, hence, targets it for modification to seek improved properties. In fact, Brown does not provide any activity data for Example 11 at all (see Brown, page 41, lines 1-23), nor is Example 11 disclosed as being more preferable than any of the other 51 specifically disclosed compounds. Thus, a person of ordinary skilled in the art seeking to prepare alternative quinazoline derivatives would have no reason to select this carbamoylanilino substituted compound as the starting point in preference to the many other, and more numerously exemplified, possibilities for the group X. Therefore, the examiner has not established a *prima facie* case of obviousness.

Moreover, even if the average skilled person did select Example 11 for some reason, Brown provides no motivation to replace the carbamoyl group on the aniline ring of Example 11 by selecting amido group from among the many possibilities disclosed for the group X.

Furthermore, based on Brown, the average skilled person would have no motivation to consider excluding the possibility of a methoxy substituent at the position corresponding to present $R^{3'}$. Example 11 of Brown contains a methoxy substituent at this position (and also at the adjacent position on the quinazoline ring, corresponding to present $R^{2'}$) and this feature is shared by a considerable number of the compounds exemplified in Brown, including by a large majority of the specific compounds listed as preferred compounds of the invention on pages 29-30 of Brown, including an especially preferred compound 6,7-dimethoxy-4-[3-methyl-4-(2-pyridylmethoxy)anilino]quinazoline listed on page 30 at lines 14-17. If anything, therefore, Brown teaches towards having methoxy substituents at *both* the 6 and 7 positions of the ring (corresponding to present $R^{2'}$ and $R^{3'}$), certainly for compounds having a carbamoyl attached to the aniline group since the only compounds with carbamoyl attached to the aniline group have also have a methoxy substituent at both the 6 and 7 positions (see Example 11 on page 54-55 and Compound 27 in Table I on page 59 of Brown).

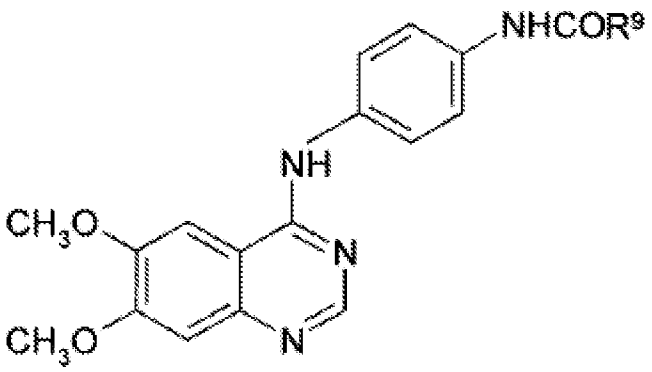
The Examiner argues in the present Official Action that the proviso for $R^{3'}$ is insufficient to overcome the equivalency teaching on the grounds that Brown lists the same substituents for R^1 at the 6- and 7- positions and these read on to the instant X^1-$R^{15'}$. However, this does not

overcome the clear teaching from Example 11 of Brown to have a methoxy group at both these ring positions when the aniline ring is substituted by a carbamoyl group. If the Examiner's reasoning that carbamoyl and amido are equivalent and further that the values for R^1 are interchangeable, it would have been expected that compounds of the present invention having a group X^1-$R^{15'}$ which is not methoxy at $R^{3'}$ would have similar activity to compounds substituted with methoxy at $R^{3'}$. However, compounds of the present invention having a group X^1-$R^{15'}$ which is not methoxy at $R^{3'}$ exhibit particularly advantageous activity against aurora A kinase as is demonstrated by the results presented in the present specification at pages 267-272 for the compound of Example 101 (from Table 4, page 37 of the present specification).



Example 101: R^9 = phenyl

compared to the compound of Example 1 (Table 1, page 34) which is now excluded from the present scope of claim).



Example 1 : R^9 = phenyl

Compound 1 gave superior results in an *in vitro* aurora2 kinase inhibition assay (see page 267-269 of the present specification) and in two *in vitro* cell proliferation assays (see pages 269-271 of the present specification). Only with the benefit of hindsight could a person of ordinary skill in the art select Example 11 from among the 51 exemplified compounds in Brown and choose groups for position 7 of the quinazoline ring that do not include a methoxy group. Therefore, in view of the above amendments and remarks, Applicants respectfully request that the rejection of claim 20, and the claims depending therefrom, under 35 U.S.C. § 103(a) as being unpatentable over Brown be reconsidered and withdrawn.

Conclusion

The above amendments have been made without prejudice to Applicants' right to prosecute any cancelled subject matter in a timely filed continuation application.

Applicants believe the application is in condition for allowance, which action is respectfully requested.

A petition for a 3 month extension of time is being filed herewith, the Commissioner is hereby authorized to charge any deficiency in the fees or credit any overpayment to deposit account No. 50-3231, referencing Attorney Docket No. Z70599-1P US.

Please charge any deficiency in the fees or credit any overpayment to deposit account No. 50-3231, referencing Attorney Docket No. Z70599-1P US.

Respectfully submitted,

/Theresa Devlin/

Name: Theresa Devlin
Dated: 12 December 2007
Reg. No.: 45361
Phone No.: 781-839-4969
Global Intellectual Property, Patents,
AstraZeneca R&D Boston,
35, Gatehouse Drive,
Waltham,
MA 02451